Quality of Life Affected by More than Renal Function in Patients with ADPKD

Recent studies have suggested that quality of life among patients with chronic kidney disease (CKD) depends on factors such as anemia and cardiovascular disease in addition to kidney function. In autosomal dominant polycystic kidney disease (ADPKD), anemia and cardiovascular disease are less frequent than in other kidney diseases, a possible indicator that other disease-specific factors may contribute to impairment of quality of life in patients with ADPKD.

ADPKD is characterized by progressive renal cyst development, leading to enlarged kidneys, kidney failure, and end-stage renal disease. Clinical symptoms appear to be a function of liver and kidney size, and are not primarily related to decline in kidney function. It is known that enlargement of the kidney occurs prior to decline in kidney function and severe polycystic liver disease may occur in early stage ADPKD, indicating the possibility that physical manifestations of ADPKD are present prior to detection of deficits in renal function, adversely affecting quality of life.

Joost PH Drenth, MD, PhD, and colleagues in the Netherlands recently conducted a systematic review and meta-analysis to examine the effect of ADPKD on quality of life. The researchers also assessed the effect of the

Warfarin Therapy Effective and Safe in Older Adults with Reduced Kidney Function

Approximately 10% to 15% of adults worldwide are affected by chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². In the patient population with CKD, the leading cause of death is cardiovascular disease, and the risk for stroke is four to 10 times greater than that in the general population. The incidence and prevalence of atrial fibrillation (AF), a major risk factor for stroke, increase as kidney function declines.

In the broader AF population, warfarin is effective in reducing the risk of embolic stroke. However, due to an increased risk for bleeding with use of warfarin, it is unclear whether use of warfarin in patients with CKD retains the risk-benefit ratio of those without CKD. There are few data on the efficacy of warfarin in CKD patients; most trials have excluded patients with CKD. Recent larger studies have conflicting results, with some reporting better stroke and survival outcomes with use of warfarin regardless of kidney function, while others reported equivalent or worse outcomes of warfarin therapy among patients on dialysis.

Recovery Times in Hemodiafiltration and High-Flux Hemodialysis

Both duration and quality of life are adversely affected by the presence of end-stage renal disease (ESRD); worldwide, approximately 1.9 million people receive renal replacement therapy. Intermittent renal replacement therapy is essential for many patients with ESRD. In the developed world, extracorporeal treatments for ESRD such as hemodialysis and hemodiafiltration are more prevalent than peritoneal dialysis.

While observational data have suggested that hemodiafiltration is beneficial, data from randomized controlled trials that compared hemodiafiltration with hemodialysis have shown mixed results. Post hoc analyses have indicated that hemodiafiltration has superior cardiovascular and mortality outcomes limited to patients receiving the highest convection volumes. However, high convection volumes may not be possible in patients with suboptimal vascular access and/or time constraints associated with dialysis provision.
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The target blood pressure in patients with chronic kidney disease (CKD), both with diabetic and non-diabetic CKD, remains controversial. In early September 2017, a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies conference will convene in Edinburgh, Scotland, to address blood pressure (BP) management in CKD patients, including questions related to the BP goal. What should the target BP be? How should elderly and frail CKD patients be treated compared with younger patients? Should the BP targets for diabetic and non-diabetic patients be the same? Should diastolic BP be taken into account when treating? An analysis by Cheung et al of CKD patients within the Systolic Blood Pressure Intervention Trial (SPRINT), recently published in the Journal of the American Society of Nephrology (JASN), will be grist to the mill for various opinion leaders in the KDIGO conference.

SPRINT recruited 9361 subjects with systolic BP of ≥130 mm Hg and an increased cardiovascular risk, but without diabetes, to a systolic BP target of <120 mm Hg (intensive treatment) or a target of <140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

Among the 2646 CKD subjects enrolled in the SPRINT study, 1330 subjects with CKD were assigned to the intensive BP group (systolic BP target of <120 mm Hg) and 1316 CKD subjects were assigned to the standard group (systolic BP target of <140 mm Hg). The mean age of participants was approximately 72 years with 44% over the age of 75 years. Nearly two thirds of enrolled CKD patients were non-Hispanic whites, but other racial types were well represented. The mean systolic/diastolic BP at baseline was, on average, approximately 139/75 mmHg. Participants had a median follow-up of 3.3 years.

Among the subjects with CKD, the primary composite cardiovascular outcome occurred in 112 of the intensive group and in 131 of the standard group. The number-needed-to-treat to prevent a primary composite outcome was 993, with a very whisper of side effects. The SPRINT CKD analysis also reported no significant benefit of intensive BP control in elderly and frail patients, being careful to slowly calibrate down the BP and bailing out at a higher BP at the very whisper of side effects.

The bottom line: intensive treatment of CKD patients resulted in a substantial decrease in the primary CVD outcome and all-cause death regardless of baseline CKD stage. And, this benefit seemed more pronounced among elderly patients (age≥75 years). Furthermore, treatment was worth it when one balanced benefit and risk. Lastly, in order to effectively achieve blood pressure reduction in the intensive treatment arm, multiple BP medications are needed—60% of subjects were on three or more medications.

How should this analysis impact clinical practice? I will aim for a SBP of 120 mmHg or lower in non-diabetic CKD patients, regardless of CKD stage. However, I plan to remain cautious with aggressive BP control in elderly and frail patients, being careful to slowly calibrate down the BP and bailing out at a higher BP at the very whisper of side effects.

REFERENCE

TAKEAWAY POINTS

- Data on the effectiveness and safety of warfarin therapy among patients with atrial fibrillation and reduced kidney function demonstrate conflicting results.

- In a community-based retrospective cohort study in Alberta, Canada, researchers sought to determine whether the comparative effectiveness of warfarin therapy and safety differ across categories of kidney function.

- In this study cohort, there was an association between initiation of warfarin therapy and a lower 1-year risk for the composite outcome of all-cause death, ischemic stroke, or transient ischemic attack across all categories of kidney function.

Min Jun, MScMed (ClinEpi), PhD, and colleagues recently utilized a population-based propensity score-matched cohort of older adults with AF to determine whether there were differences in the comparative effectiveness of warfarin therapy across categories of kidney function. The researchers reported results of the retrospective cohort study in the *American Journal of Kidney Diseases* [2017;69(6):734-743].

The primary outcomes of interest were, within 1 year of initiation of warfarin therapy (or the matched date for nonusers): (1) the composite of all-cause death, ischemic stroke, or transient ischemic attack (also assessed as separate end points); and (2) the first hospitalization or visit to the emergency department for a major bleeding episode, defined as an intracranial, upper or lower gastrointestinal, or other bleeding.

The researchers used province-wide laboratory and administrative data in Alberta, Canada, to identify adults ≥66 years of age with new AF and a measurement of kidney function. Exclusion criteria were patients with long-term dialysis use or kidney transplant recipient. Propensity scores were used to construct a matched-pairs cohort of patients with AF who did and did not have a prescription for warfarin with 60-days surrounding the diagnosis of AF.

The data identified a total of 21,830 adults with newly diagnosed AF between May 1, 2003, and March 31, 2012. Of those patients, 9852 filled a prescription for warfarin during the period 30 days before (n=1175) or after (n=8677) the newly diagnosed AF record and had one or more outpatient serum creatinine measurement. Of those patients, 75% (n=7446) were matched 1:1 to similar patients with no dispensed warfarin prescription during the same period.

The final cohort included 14,892 patients. Mean time between the incident AF and the first prescription for warfarin was 6.7 days. Before propensity score matching, there was moderate imbalance in the distribution of some covariates by warfarin use: the proportion of patients with certain comorbid conditions was lower among warfarin users than among nonusers. Following propensity score matching, balance was achieved across all included covariates. Mean age of the cohort was 78.1 years, 49.6% were men, and 42.4% had eGFRs <60 mL/min/1.73 m².

During follow-up of 1 year, 14.1% of patients (n=2104) developed a composite outcome; 6.9% (n=1023) had a major bleeding episode. When assessed as individual outcomes, there were 567 ischemic strokes or transient ischemic attack events and 1647 deaths. In both warfarin users and nonusers, rates of the composite outcome and major bleeding increased with declining eGFR.

Within each eGFR category, the event rate of the composite outcome was lower in warfarin users compared with nonusers. When individual outcomes of the composite outcome were examined, similar results were observed.

In patients with eGFR of 60 to 89 mL/min/1.73 m², there were significant differences in the incident rate of major bleeding across warfarin users and nonusers; there were no significant differences across the remaining categories of eGFR.

Compared with nonuse, there was an association between use of warfarin and 36% to 46% lower risk for the composite outcome, within each eGFR category: adjusted hazard ratios [HRs] (95% confidence intervals [CIs]) for eGFR categories ≥90, 60-89, 45-59, 30-44, and <30 mL/min/1.73 m² were 0.59 (0.35-1.01; P=.06), 0.61 (0.54-0.70; P=.001), 0.55 (0.47-0.65; P=.001), 0.54 (0.44-0.67; P=.001), and 0.64 (0.47-0.87; P=.005), respectively. There was no modification by eGFR category in the magnitude of the relative risk associated with warfarin therapy (P=.8).

When assessed as individual outcomes, there was a lower risk for ischemic stroke or transient ischemic attack across categories of eGFR with warfarin use (statistical significance was not reached in two categories).

There was no significant increase in the risk for major bleeding associated with warfarin therapy by eGFR category, with the exception of eGFR 60 to 89 mL/min/1.73 m²: compared with nonuse, there was an association between warfarin therapy and a 36% higher risk for major bleeding in that eGFR category (HR, 1.36, 95% CI, 1.13-1.64; P=.001).

The researchers cited some limitations to the study, including estimation of the propensity score (based on the likelihood of a patient with AF to receive warfarin therapy), which may have contributed to inclusion of patients at higher risk for stroke and lower risk for bleeding, leading to a relatively lower risk for major bleeding in the study. In addition, matching led to the exclusion of 24% of eligible patients with a dispensed warfarin prescription (most of whom were excluded due to missing data on outpatient serum creatinine level). Finally, the study does not include an assessment of the effectiveness and safety of warfarin use among patients on long-term dialysis therapy or on kidney transplant recipients.

In conclusion, the researchers said, “In our cohort of older adults with AF, initiation of warfarin therapy was associated with significantly lower 1-year risk for the composite outcome of all-cause death, transient ischemic attack, or ischemic stroke compared to nonuse, across all assessed levels of kidney function, with no appreciable increase in bleeding risk except for those with eGFRs of 60 to 89 mL/min/1.73 m². Our results suggest that warfarin therapy may have a favorable risk-benefit profile among patients with AF with non–dialysis-dependent CKD. Randomized controlled trials are needed to verify these findings.”
markers of disease severity—renal function, renal volume, and liver volume—on quality of life for patients with ADPKD. They reported results online in BMC Nephrology [doi:10.1186/s12882-017-0578-6].

Eligibility criteria for included studies were (1) cohort studies and randomized controlled trials; (2) adult patients >18 years of age, with a diagnosis of ADPKD; and (3) use of a patient-reported outcome to reflect quality of life. Exclusion criteria were studies that used a patient-reported outcome without summary score of individual questions, studies that investigated quality of life with a one-item visual analogue scale only, longitudinal intervention studies that provided no baseline quality of scores, and studies that did not report original data.

The researchers searched the electronic databases of EMBASE, MEDLINE, and Web of Science. They also searched for conference abstracts in abstract books of the American Society of Nephrology, the World Congress of Nephrology, and the European Renal Association–European Transplant and Dialysis Association published between August 2012 and August 2015, as well as unpublished studies in the database of clinicaltrials.gov.

The primary outcome of interest was summary quality-of-life score measured with a patient-reported tool at baseline. Studies were included in the meta-analysis and meta regression if they used a patient-reported tool at baseline. Of those, 11 matched the inclusion criteria, the final meta-analysis included nine studies. The majority of the nine (n=7) were longitudinal intervention studies, including three that utilized a randomized controlled design. Eight of the studies used the Short Form Health Survey (SF-36), both the physical component scale score and a mental component scale score, as patient-reported outcome and one used the Kidney Disease Improving Global Outcomes-SF-1.3, a questionnaire that combines the SF-36 and 43 kidney disease-specific questions.

The nine included studies represented 1623 non-dialysis patients; at least 753 patients had CKD stage 1-2 and 478 had CKD stage 3-4; 363 patients had insufficient data on renal function, precluding identifying CKD stage for that subgroup. One study did not provide renal function data on the 37 participants, resulting in 1594 patients eligible for assessment of the impact of renal function on quality of life. The mean physical component scale of individuals with ADPKD was 45.7 points (95% confidence interval [CI], 42.7-48.7), although there was significant heterogeneity (I² 95.4%; P < .001); the mean physical component scale of the general population was 50 points (95% CI, 49.6-50.4; P < .001). Patients with ADPKD scored 47.8 points on the mental component scale (95% CI, 45.7-49.8), again with large heterogeneity (I² 90.7%; P < .001), compared with 50 points in the general population (95% CI, 49.6-50.4; P < .001).

Quality of life of patients with ADPKD remained significantly lower when compared with age-corrected reference values: among participants age 35 to 44 years, physical component scale was 52.2 points (95% CI, 51.3-52.8; P < .001) and mental component scale was 49.9 points (95% CI, 49.1-50.7; P < .001).

Assessment of the relationship of markers of disease severity on quality of life among patients with ADPKD found a negative impact of larger liver volume on the physical component scale. There was no significant effect of renal function, kidney volume, and total liver and kidney volume on the physical component scale. On the mental component scale, larger liver volume and total liver and kidney volume had significant impact; there was no impact of renal function and kidney volume on mental component scale scores.

In noting limitations to the study, the researchers cited the lack of complete data on the values of all disease severity markers, as well as the inability to include all potential modifiers of quality of life in ADPKD. In addition, data on quality of life was collected solely on a generic patient-reported outcome, which may be less sensitive to detect disease burden compared with disease-specific measures.

In conclusion, the researchers said, “There are limited representative data available on the impact of disease severity markers on quality of life in ADPKD. Existing data showed that quality of life of non-dialysis ADPKD patients is impaired compared with the general population. Large liver volume was the most important factor that diminishes quality of life.”

—Joost PH Drenth, MD, PhD

The primary outcome of interest was summary quality-of-life score measured with a patient-reported tool at baseline.
Delayed recovery times were longer with hemodiafiltration compared with hemodialysis: median of 150 minutes versus 137 minutes; \( P<.001 \).

The length of recovery time after dialysis is an important outcome measure affecting health-related quality of life reported by patients. Further, data from DOPPS (Diagnosis Outcomes and Practice Patterns Study) have shown an association between longer postdialysis recovery time and increased mortality. James R. Smith, MBChB, and colleagues in Scotland performed a patient-blinded randomized crossover study of patient-reported recovery time to determine whether recovery time differs between hemodialysis and hemodiafiltration. The researchers reported results in the American Journal of Kidney Disease [2017;69(6):762-770].

The outcomes of interest were post-treatment recovery time, symptomatic hypotension events, dialysis circuit clotting events, and biochemical parameters. Measurements included patient-reported recovery time in minutes, incidence of adverse events during treatments, hematology and biochemistry results, and responses to a quality-of-life questionnaire. The study intervention was 8 weeks of hemodialysis followed by 8 weeks of online postdilution hemodiafiltration or vice versa. The total study cohort included 100 patients who were randomly assigned to receive hemodialysis and then hemodiafiltration or hemodiafiltration and then hemodialysis. Mean age was 65 years, 39\% were women, and 99\% were white.

Treatment time and blood flow rate remained constant between hemodialysis and hemodiafiltration. Ultrafiltration volumes were similar and the mean convection volume for hemodiafiltration treatments was 20.6 L. While participants were receiving hemodiafiltration, pretreatment systolic blood pressure was lower (143 vs 145 mm Hg; \( P=.03 \)); however, the difference was not seen post treatment.

For 92\% of all sessions, data on recovery time were available. Of the available data, recovery time for one-third of the sessions was reported as zero minutes (immediate), resulting in a bimodal distribution. To account for this, separate models were used to analyze immediate and delayed (>0 minutes) recovery times, then joined to obtain an overall \( P \) value. This demonstrated no overall difference in recovery time between hemodiafiltration and hemodialysis (median values of 47.5 minutes and 30 minutes, respectively; \( P=.9 \)). However, individual models for immediate and delayed recovery time showed that patients were more likely to report immediate recovery while receiving hemodiafiltration treatment. Delayed recovery times were longer with hemodiafiltration compared with hemodialysis: median of 150 minutes versus 137 minutes; \( P<.001 \).

There was an association between hemodiafiltration and an increased rate of symptomatic hypotension compared with hemodialysis (8.0\% vs 5.3\%; relative risk [RR], 15.2; 95\% confidence interval [CI], 1.2-1.9; \( P<.001 \)). While on hemodiafiltration, three patients had increased dosing in antihypertensive medications, as did one patient on hemodiafiltration. Dosing was reduced in three patients while on hemodialysis and in one patient while on hemodiafiltration therapy.

The intradialytic tendency to clotting was higher during hemodiafiltration than during hemodialysis: 1.8\% versus 0.7\%; RR, 2.7; 95\% CI, 1.5-5.0; \( P=.002 \).

There were no significant differences between the two treatments in the prespecified laboratory measurements. There were small but statistically significant differences in serum albumin (3.2 vs 3.3 g/dL for hemodiafiltration and hemodialysis, respectively; \( P<.001 \)) and chloride levels (101 vs 100 mEq/L for hemodiafiltration and hemodialysis, respectively; \( P<.02 \)).

To measure quality of life, patients completed Kidney Disease Quality of Life—Short Form, version 1.3, questionnaires during the study. At baseline, the patients scored physical health lower than mental health. After 8 weeks of each treatment, there was no difference in physical health composite scores or mental health scores.

Study limitations cited by the authors included the single-center design of the study, as well as the predominance of patients with European ancestry. Further, it is possible that the nursing staff’s longer term experience with hemodiafiltration compared with hemodialfiltration may have had an influence on the results.

In conclusion, the researchers said, “Debate remains regarding the clinical case for hemodiafiltration over hemodialysis. Patient preference and shared decision making are increasingly prioritized in clinical practice, and these data may further inform the discussion around choice of extracorporeal treatments.”

### American Transplant Congress

**Obinutuzumab Safe and Effective for B-Cell Depletion in Transplant Candidates**

Chicago—in allosensitized patients with end-stage renal disease (ESRD), the efficacy of rituximab for desensitization and enabling kidney transplantation is limited; tissue B-cell depletion is incomplete. Robert R. Redfield III, MD, and colleagues recently conducted an open-label phase 1b study to test the hypothesis that obinutuzumab may be more effective for desensitization than rituximab. Obinutuzumab is a glycoengineered type 2 anti-CD20 monoclonal antibody that displays increased in vitro and in vivo B-cell depletion compared with rituximab.

The study was designed to examine the safety, pharmacokinetics, and pharmacodynamics of obinutuzumab in hypersensitized patients with ESRD who were awaiting kidney transplantation. Results were reported during a poster session at the 2017 American Transplant Congress in a poster titled Emerging Safety and Tolerability of Obinutuzumab, a Type 2 Anti-CD20 Monoclonal Antibody for the Desensitization of Renal Transplant Candidates.

Patients were assigned to one of two groups: cohort one (\( n=5 \)) received one infusion of 1000 mg obinutuzumab followed by a high-dose intravenous immunoglobulin (IVIG) on days 22 and 43; cohort two (\( n=20 \)) received two infusions of 3000 mg obinutuzumab followed by high-dose IVIG on days 22 and 43. Nine patients received a total of three infusions; the third dose occurred at the time of kidney transplantation (\( n=5 \)) or at week 24 (\( n=4 \)). Conventional flow cytometry (FC) and high-sensitivity FC were used to monitor peripheral blood B-cell counts. A central laboratory was used to analyze anti-human leukocyte antibodies (anti-HLA). When the last patients reached 14 weeks after the final obinutuzumab infusion, a safety and tolerability data cut was taken.

Twenty-three of the 25 patients were women. Mean age was 50 years, mean waiting time was 5.5 years, and calculated reactive antibody values were 91. One patient in cohort two withdrew because kidney transplantation occurred before administration of the second dose of obinutuzumab.

At week 3, 24 of the remaining 24 patients and 22 of the 24 displayed B cells at or below the lower limit of quantification by FC and high-sensitivity FC. Obinutuzumab was well tolerated. Manageable grade 1 and 2 infusion-related reactions were the most common adverse events; the reactions did not prevent completion of the obinutuzumab infusions.

Seven of the 25 patients had serious adverse events, all of which were infections that resolved with standard care treatment. Of the 24 patients who completed the protocol, seven have received a kidney transplant to date. Ongoing analysis of treatment effects on anti-HLA alloantibodies is occurring.

In conclusion, the researchers said, “Exposure to obinutuzumab resulted in substantial peripheral B-cell depletion at both dose levels. Emerging experience with obinutuzumab indicates acceptable tolerability in patients with end-stage renal disease undergoing desensitization.”

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INDICATION
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IMPORTANT SAFETY INFORMATION
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• Patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major gastrointestinal (GI) surgery, or with a history of hemochromatosis or other diseases with iron accumulation have not been included in clinical studies with Velphoro. Monitor effect and iron homeostasis in such patients.
• In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%).
• Velphoro can be administered concomitantly with oral calcitriol, ciprofloxacin, digoxin, enalapril, furosemide, HMG CoA reductase inhibitors, hydrochlorothiazide, losartan, metoprolol, nifedipine, omeprazole, quinidine and warfarin. Take doxycycline at least 1 hour before Velphoro. Velphoro should not be prescribed with oral levothyroxine.

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CONTRAINDICATIONS
None.

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ADVERSE REACTIONS
In a parallel design, fixed-dose study of 6 weeks duration, the most common adverse drug reactions to Velphoro chewable tablets in hemodialysis patients included discolored feces (12%) and diarrhea (6%).

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care North America at 1-800-323-5188 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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FRESENIUS MEDICAL CARE
Treating Children and Adolescents with ESRD: A Guide for Nephrologists

It is rare for children to be diagnosed with end-stage renal disease (ESRD); there are approximately 8500 children with ESRD in the United States, according to the most recent US Renal Data System report. Each year, approximately 1500 children in the United States develop ESRD; two-thirds of those patients initiate treatment with hemodialysis and one-third initiate treatment with peritoneal dialysis.

Following initiation of therapy, less than half of all children are maintained on peritoneal dialysis, and a small majority are maintained on hemodialysis therapy. Infants and young children are more likely to be maintained on peritoneal therapy, while older adolescents are more likely to be treated with hemodialysis therapy.

ESRD is a chronic disease that affects all aspects of maturation to adulthood and carries a need for a lifetime of complex and specialized care, making children with ESRD a particularly vulnerable patient population. Adding to the complexity of managing children with ESRD is the need for a parent or caregiver in all aspects of the child’s medical treatment.

Deepa H. Chad, MD, MHSA, and colleagues recently authored a position paper titled “Dialysis in Children and Adolescents: The Pediatric Nephrology Perspective,” offering guidance for providers, facilities, and institutions on the components of care required for children receiving dialysis. The paper, endorsed by the Council of the American Society of Pediatric Nephrology, was published in the American Journal of Kidney Diseases [2017;69(2):278-286].

For each child on dialysis therapy, there needs to be an interdisciplinary dialysis team that works together to plan and coordinate all aspects of individualized care for the child. The team should include a nephrologist, a nurse, a social worker, an administrator, and a dietitian. Other possible team members include child life specialists, teachers, and psychologists who play a key role in the child’s day-to-day ESRD treatment and interact with the child and the parent or caregiver. Because many children with ESRD have comorbid urinary outlet disorders, a pediatric urologist with surgical expertise may be needed to prepare the child medically for kidney transplantation.

In dialysis units with personnel with no specific pediatric training, access to consultations with colleagues who are trained to care for children and aware of current standards of pediatric dialysis care is necessary. Referral to a pediatric kidney transplantation center is also required.

The interdisciplinary team should also involve the family as an integral part of care planning and be aware of the ways the recommended therapy affects the family unit. The team should also involve the child in a developmentally appropriate manner and work to ensure that parents and caregivers understand the rationale for recommendations about therapy modalities.

Dialysis access placement is crucial for pediatric patients to maximize the potential for future dialysis access if and when needed. As the child moves closer to requiring renal replacement therapy, access should be a prior-

continued on page 10
Aurina plans to initiate a phase 3 clinical trial (AURORA) in 2017. This will be a 52-week double-blind placebo controlled study conducted globally in approximately 320 patients to demonstrate that VCS when added to standard of care can increase overall renal response (remission) rates in the presence of low steroids. The researchers said.


The primary end point of interest was complete remission at 24 weeks. Secondary end points included partial response, time to complete remission or partial response, and week 48 remission rates. The primary and all secondary end points were met at 24 weeks in the two treatment groups. At week 24, both doses of VCS had statistically significant improvement compared with placebo. For patients who achieved complete response, median time to complete response was 7.3 weeks, compared with 12.1 weeks among patients in the placebo group. At 48 weeks, there was a rapid time to complete response for both doses (P < 0.001).

VCS at 23.7 mg was well tolerated and demonstrated higher complete remission versus placebo, higher partial response, and faster time to complete response: 23.7 mg is the appropriate dose to advance into Phase 3. The AURA phase 2b results support the advancement of VCR into a phase 3 clinical trial and will serve as one of two registration studies for submission of a New Drug Application to the FDA.

For each child on dialysis therapy, there needs to be an interdisciplinary dialysis team that works together to plan and coordinate all aspects of personalized care for the child. The team should include a nephrologist, a nurse, a social worker, an administrator, and a dietitian. Better care is needed for the better the chances of ongoing favorable outcomes. All dialysis facilities caring for children need to be cognizant of the needs of their pediatric patients across all domains of dialysis care, with the involvement of a competent and pediatric-focused interdisciplinary dialysis team and the willingness to involve other resources as needed."
Dialysate Potassium Level and Adverse Events in Patients on Hemodialysis

In patients requiring hemodialysis, sudden death is a leading cause of death; 27% of all deaths in that patient population are attributable to arrhythmic mechanisms. In patients on maintenance hemodialysis three times a week, these events tend to cluster in the period just prior to the first dialysis session of the week when fluid overload and levels of various uremic toxins are at their peak, and in the period during and immediately after hemodialysis sessions.

Patients with kidney failure often experience hyperkalemia due to diminished renal potassium excretion that causes disturbances in heart rhythm and cardiac arrest in extreme cases, and high predialysis serum potassium level is a risk factor for sudden death and all-cause mortality in hemodialysis patients.

There is no clear consensus on the optimal electrolyte concentration in the dialysate; it is unclear whether there are differences in patient outcomes among those treated with a dialysate potassium concentration of 3 mEq/L compared with 2 mEq/L. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative does not provide recommendations for dialysate potassium concentrations in cardiovascular disease guidelines; however, several recent reviews are in agreement that dialysate potassium concentration <2 mEq/L should be avoided, particularly in patients with high levels of potassium predialysis, to avoid a rapid decrease in plasma potassium levels.

Researchers, led by Angelo Karaboyas, MS, recently conducted a prospective cohort study designed to leverage data from the international cohort of in-center hemodialysis patients in the DOPPS (Dialysis Outcomes and Practice Patterns Study) to assess risk of different potassium prescriptions overall and among patients with different levels of serum potassium.

The researchers also assessed associations between predialysis serum potassium levels and outcomes, and an association between dialysate potassium concentrations and serum potassium levels. Results of the study were reported in the American Journal of Nephrology Times | July/August 2017.

National Kidney Foundation

Uncontrolled Gout among Patients with Chronic Kidney Disease

Orlando—Gout, caused by primarily by elevated serum uric acid in the blood, is the most common form of inflammatory arthritis. Recommendations in guidelines from the American College of Rheumatology call for lowering serum uric acid levels to <6 mg/dL for all patients with gout. Elevated serum uric acid is also associated with chronic kidney disease and results of previous studies suggest that urate-lowering therapy, predominantly xanthine oxidase inhibitors (XOIs), can slow progression of renal disease.

Jean J. Lim, MD, and colleagues recently conducted a study to examine the prevalence of CKD among adult gout patients in the United States; both controlled and uncontrolled, stratified by XOIs treatment status. Controlled gout was defined as serum uric acid level <6 mg/dL and uncontrolled as serum uric acid level ≥6 mg/dL. Study results were reported during a poster session at the NKF 2017 Spring Clinical Meetings in a poster titled Prevalence of CKD and Uncontrolled Gout among US Adults: Results from NHANES 2007-2012.

The researchers utilized data from the National Health and Nutrition Examination Survey (NHANES) 2007-2012. NHANES is conducted by the National Center for Health Statistics and is used to estimate the disease prevalence of the non-institutionalized US population. The study sample included respondents with valid data of gout status, sex, race/ethnicity, serum uric acid and serum creatinine levels; individuals <20 years of age were excluded.

Study measures included respondents with reported gout, uncontrolled gout, and Charlson comorbidity index. Other study measures were gout, uncontrolled gout, gout medication, hypertension, obesity, diabetes, cardiovascular disease, demographic variables, and health insurance status.

Of the 15,868 respondents in NHANES 2007-2012, 715 individuals had been told a physician that they had gout. Those respondents represented an estimated total of 7.7 million US individuals with gout (US prevalence of 3.7%). Among the estimated gout population, 74% (n=5.7 million) had normal to stage 2 CKD, 15% (n=1.1 million) had stage 3a CKD, and 11% (n=0.8 million) had stage 3b to 5 CKD. Of those with gout, 22% with normal to stage 2 CKD, 42% with stage 3a CKD, and 44% with stage 3b to 5 CKD were currently being treated with an XOI; most of those taking an XOI were taking allopurinol.

Comorbidities in the overall estimated gout population were obesity (54%), diabetes (24%), hypertension (69%), and cardiovascular disease (22%). Those with more severe CKD had higher proportions of hypertension and cardiovascular disease.

Regardless of CKD stage, the majority of gout was uncontrolled: 63% in normal to stage 2 CKD, 62% in stage 3a CKD, and 72% in stage 3b to 5 CKD. In those with normal to stage 2 CKD, 44% of those taking an XOI had uncontrolled gout and 68% of those not taking an XOI had uncontrolled gout. In the population with stage 3a CKD, 36% taking an XOI had uncontrolled gout and 80% of those not taking an XOI had uncontrolled gout. Among those with stage 3b to 5 CKD, 57% of patients taking an XOI had uncontrolled gout and 83% of those not taking an XOI had uncontrolled gout. Of the overall population taking an XOI, 34% were uncontrolled and had normal to stage 3a CKD.

In conclusion, the researchers said, “The majority of non-institutionalized US adults who self-report that they have been diagnosed with gout have uncontrolled gout regardless of CKD stage, with the highest proportion of uncontrolled gout among those patients who have stage 3b to 5 CKD. Among those estimated gout patients who are taking an XOI, 34% are uncontrolled and have normal to stage 3a CKD, and therefore, may benefit from alternative treatment options indicated for their CKD stage.”


continued on page 12
The participants were SS,183 patients from 20 countries in DOPPS phases one to five (1996-2015). Cox regression was used to estimate the association between dialysis potassium concentration and all-cause mortality as well as an arrhythmia composite outcome (arrhythmia-related hospitalization or sudden death), adjusting for potential confounders. All SS,183 patients were included in the primary analysis of all-cause mortality; 45,511 participants were included in the analyses of arrhythmia composite outcomes (9672 patients were in facilities that did not report cause of events).

Mean serum potassium level was highest in Russia (5.3 mEq/L) and lowest in the United States (4.6 mEq/L). Trend analyses revealed that during the past 20 years, serum potassium level has decreased in Europe, Australia, New Zealand, and Japan. In North America, serum potassium level has remained fairly constant during that time period. In each country, serum potassium levels collected at the first hemodialysis session of the week (Monday/Tuesday) were slightly higher than those collected midweek. (Wednesday/Thursday), the difference ranged from 0.01 mEq/L in China to 0.19 mEq/L in Germany.

During a median follow-up of 16.5 years, 24% of the SS,183 DOPPS participants died (n=13,114), resulting in a mortality rate of 16.1 per 100 patient-years. In unadjusted analysis, compared with the reference group of serum potassium level of 4.0 to 5.0 mEq/L, lower serum potassium level, but not higher serum potassium level, was associated with mortality. Following comprehensive multivariable adjustment, the association of potassium level with mortality changed to higher but not lower serum potassium level.

Of the 45,511 DOPPS participants eligible for the cause-specific outcome analysis, 7% (n=3300) had an arrhythmia composite event during follow-up. The adjusted association between serum potassium level and the composite arrhythmia outcome appeared approximately monotonic, with increased risk for patients with higher levels of serum potassium.

For the composite outcome, compared with a reference group (dialysate potassium concentrations of 2.0 to 2.5 mEq/L), the hazard ratio (HR) for mortality was 0.95 (95% confidence interval [CI], 0.90-1.00) for patients treated with dialysate potassium concentrations of 3.0 to 4.0 mEq/L, and 1.04 (95% CI, 0.97-1.11) for those treated with dialysate potassium concentrations of 1.0 to 1.5 mEq/L. Using instrumental variable methods, the HR per 1-mEq/L higher dialysate potassium concentration was 0.99 (95% CI, 0.92-1.07) for all-cause mortality and 0.96 (95% CI, 0.82-1.12) for the arrhythmia composite outcome.

Following adjustment for only DOPPS phase and country, a linear regression model revealed an inverse association between dialysate potassium concentration and predialysis serum potassium level (–0.35 [95% CI, –0.37 to –0.34] mEq/L of serum potassium per 1-mEq/L greater dialysate potassium). The inverse association remained following multivariate adjustment for confounders (–0.25; 95% CI, –0.26 to –0.24). In an instrumental variable analysis, there was a weak positive association between dialysate potassium concentration and serum potassium level (+0.09 [95% CI, +0.05 to +0.14] mEq/L of serum potassium per 1-mEq/L greater dialysate potassium).

There were some limitations to the study, including the inability to estimate the causal impact of serum potassium level and dialysate potassium concentration on the risk for adverse events due to the study’s observational design. In addition, there were no data for postdialysis serum potassium levels, and only prescribed dialysate potassium information was available.

In conclusion, the researchers said, “Despite the limitations, these findings have important implications for dialysate potassium prescribing practices and future research. We did not find evidence supporting a clinically meaningful difference in mortality or arrhythmias comparing dialysate potassium concentrations of 3.0 versus 2.0 mEq/L at any level of predialysis serum potassium and thus cannot provide a recommendation for any immediate changes in practice. Long term, our results support equipoise for future research of an easily modifiable practice pattern in a randomized setting. As previously reported, high predialysis serum potassium level was associated with increased risk for adverse events. However, we observed minimal association between dialysate potassium concentration and serum potassium measured before dialysis. In combination, these results suggest that approaches other than altering dialysate potassium concentrations (eg, education on dietary potassium sources and prescription of potassium-binding medications) may merit further attention to reduce risks associated with high serum potassium levels.”

**Care Coordination Program Improved Outcomes and Reduced Costs**

Cigna commercial medical beneficiaries at highest risk of progression of CKD from stage 4 to stage 5 were identified using an algorithm. Those randomized to the intervention group received an evidence-based assessment tool, education, and follow-up. Nephrologists and other providers were engaged and weekly rounds were conducted. The primary outcome measures were hospital admissions, visits to the emergency department (ED), dialysis, fistula placement, and total medical costs. Follow-up continued through July 2013. Eleven million beneficiaries were screened for eligibility; of those, 7720 with stage 4 CKD were randomized between January 2012 and October 2012. There were 3861 beneficiaries randomized to the intervention group; of those, 3055 received the case management intervention. A control group (n=3859) received standard care. At baseline, there were no differences in demographic and clinical characteristics between the two groups.

Outcomes examined included number of hospital admissions, number of ED visits, number of nephrologist visits, number of dialysis visits, fistula placement, total claim cost, and per member per month cost. There were no statistically significant pre-period differences between the intervention and control groups.

Compared with the control group, the intervention group had slightly fewer hospital admissions and slightly more visits to nephrologists and EDs; the differences were not statistically significant. Those in the intervention group were 12% more likely to have an arteriovenous fistula placement (P=0.004) than those in the control group.

Beneficiaries in the intervention group had savings of $199 per member per month compared with those in the control group. This difference equated to 6% lower total medical costs in the intervention group (P=0.041).

“Our findings support the value of care coordination between nephrologists, providers, and payer case managers in improving outcomes and reducing total medical costs among beneficiaries at risk for CKD progression from stage 4 to 5,” the researchers said.

Risk Factors for Development of ESRD in Patients with IgA Nephropathy

IgA nephropathy (IgAN) accounts for 45.36% of primary glomerular disease in China; it is also a leading cause of end-stage renal disease (ESRD). Approximately 30% of patients with IgAN progressed to ESRD within 10 to 20 years; however, in some patients, disease progression was more rapid, with ESRD occurring within 10 years. Previous studies found associations between various clinical and pathological markers, including proteinuria, hypertension, decreased estimated glomerular filtration rate (eGFR) at time of biopsy, and MEST score (four histologic components: mesangial [M] and endocapillary hypercellularity [E], segmental sclerosis [S], and interstitial fibrosis/tubular atrophy [T]), and renal outcomes.

In this study, the researchers conducted a single-center case-control study to examine the prognostic value of specified clinical data in predicting the development of end-stage renal disease (ESRD) in individuals with severe IgA nephropathy (IgAN). The case group also had more rapid, with ESRD occurring within 10 to 20 years; however, in some patients, disease progression was more rapid, with ESRD occurring within 10 years.

The case group had higher levels of serum creatinine, UA, TC, 24-hour urinary protein, and the proportion of hypertension at biopsy compared with the control group ($P<.05$). Hemoglobin, Alb, eGFR and the proportion of macro-hematuria were lower in the control group than in the case group ($P<.05$). When analyzed with multivariate logistic regression, M1, eGFR at biopsy, TA-UA, and TA-Hb were independent risk factors for the development of ESRD among patients with IgAN.

In univariate logistic analysis, there was an association between M1, S1, T1 or T2, impaired renal function, high UA, TC, 24-hour urine protein levels, hypertension history at biopsy, and high TA-UA, TA-TC and increased risk for development of ESRD. There was an association between a decreased risk of ESRD and high levels of baseline eGFR, Hb, Alb, and TA-Hb and TA-Alb during follow-up and the presence of macro-hematuria. When analyzed with multivariate logistic regression, M1, eGFR at biopsy, TA-UA, and TA-Hb were independent risk factors for the development of ESRD among patients with IgAN.

Study limitations cited by the authors included the retrospective design and a selection bias.

In summary, the researchers said, “Patients with pathological assessment of M1, T1, or T2, impaired renal function, abnormal blood biochemical parameters and hypertension at biopsy should be paid more attention, and therapies aiming to keep UA and Hb levels under control and reduce urinary protein during the follow-up are highly recommended. Pathological type M may play an important role in IgAN outcomes among [the] Chinese population.”

**Takeaway Points**

- Chinese researchers conducted a single-center case-control study to examine the prognostic value of specified clinical data in predicting the development of end-stage renal disease (ESRD) in individuals with severe IgA nephropathy (IgAN).
- In comparisons of IgAN patients with renal survival time of <10 years after renal biopsy (case group) with patients with renal survival time of >10 years, differences in time-average (TA) uric acid, hemoglobin, albumin, total cholesterol, and urinary protein between the two groups were observed.
- IgAN patients with low baseline estimated glomerular filtration rate, low TA hemoglobin, and high TA uric acid were more likely to develop ESRD.
Tolvaptan Reduces Incidence of Kidney Pain in Patients with ADPKD

Patients with autosomal dominant polycystic kidney disease (ADPKD) often experience pain, a symptom reported early in the course of the disease. The pain associated with ADPKD can be severe and a challenge to manage as well as a complication that has an adverse effect on a patient’s quality of life. ADPKD-related acute pain may be caused by cyst hemorrhage, infection, and kidney stones, often accompanied by hematuria. Chronic pain, defined as being present >4 to 6 weeks, has reported prevalence as high as 60% in this patient population.

Results from the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3:4 trial reported the renoprotective benefits of treatment with tolvaptan in a randomized controlled clinical trial setting. During 3 years of follow-up, tolvaptan (a vasopressin V2 receptor antagonist) reduced the annual rate of growth in total kidney volume from 5.5% to 2.8% (P<.001) as well as the annual rate of estimated glomerular filtration rate (eGFR) from −3.70 to −2.72 mL/min/1.73 m².

A secondary composite end point of the TEMPO trial was reduction in ADPKD-related clinical events; there was a reduction in clinical progression as assessed by that end point. This outcome was driven by two components of the composite end point: time to decline in kidney function and time to clinically significant kidney pain events.

Nick F. Casteleijn, MD, and colleagues in the Netherlands, recently conducted a secondary analysis of data from TEMPO to define what constituted a clinically significant kidney pain event by examining the intensity of medical interventions used to define them, and to assess the association of ADPKD characteristics (history of kidney pain, infection, kidney stones, or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial. The researchers also conducted an analysis of the effect of tolvaptan use on the incidence of kidney pain events and examined whether there was an association between new pain events and baseline patient characteristics. Results were reported in the American Journal of Kidney Diseases [2017;69(2):210-219].

The TEMPO 3:4 trial enrolled a total of 1445 participants. Mean age was 39 years, and 48.4% were women. By study protocol, patients had preserved kidney function: mean eGFR was 81 mL/min/1.73 m² and median total kidney volume was 1692 mL. At baseline, 50.9% of participants reported a history of kidney pain; the researchers stratified patient characteristics according to those with and without a history of kidney pain.

There was an association between having a history of kidney pain with a history of urinary tract infection, kidney stones, or hematuria. Female sex, smaller body size, and lower urinary osmolality were also significantly associated with a history of kidney pain. (For the last two variables, the absolute difference between patients with and without a history of kidney pain was small and likely not clinically relevant). Following adjustment for sex, age, height-adjusted total kidney volume, and eGFR, the characteristics remained significant.

Of the 1445 participants, 484 were randomly assigned to placebo and 961 were randomly assigned to tolvaptan. Of the placebo group, 49.4% had a history of kidney pain; of the tolvaptan group, 51.6% had a history of kidney pain.

Of the patients in the placebo group, 16.7% had an episode of kidney pain during the 3 years of the trial. There tended to be an association with a history of urinary tract infection, kidney stones, hematuria, kidney pain, and female sex with incident kidney pain events. With the exception of history of urinary tract infection, these factors remained significantly associated with kidney pain events following adjustment for age, sex, height-adjusted total kidney volume, and eGFR.

Among the group treated with tolvaptan, 10.1% had clinically significant kidney pain during the 3 years of the trial. Use of tolvaptan was associated with a significantly lower incidence of first kidney pain events compared with placebo (P<.001), with a risk reduction of 36% (hazard ratio, 0.64; 95% confidence interval, 0.48-0.86). Over time, the difference in cumulative incidence of patients having a kidney pain event between the tolvaptan group and the placebo group increased.

The researchers cited some limitations to the study: (1) the post hoc analysis design; (2) the inclusion criteria used in the TEMPO 3:4 trial; (3) the aquaretic response to tolvaptan causes polyuria, which may have resulted in under- or overestimation of pain reporting; and (4) focusing only on acute kidney pain events without investigating the effect of tolvaptan on chronic pain in patients with ADPKD.

In conclusion, this study shows that a history of urinary tract infection, kidney stones, or hematuria and female sex were associated with a history of kidney pain at baseline, as well as with incident kidney pain events during the trial. No association was found between total kidney volume and history of pain at baseline or with incident kidney pain events during the trial, indicating that kidney volume per se did not play a major role in causing pain. Tolvaptan use was associated with lower incidence of acute kidney pain events in all subgroups identified according to pain severity and independent of factors predisposing to pain incidence. The tolvaptan-induced reduction in incidence of renal complications, such as urinary tract infections, kidney stones, and hematuria, may at least in part explain the kidney pain-lowering effect of this drug,” the researchers said.
Safety and Efficacy of Belatacept as Immunosuppression in Kidney Transplant Recipients

Cyclosporine and tacrolimus, calcineurin inhibitors (CNIs), are commonly used as immunosuppressive therapy in patients who have undergone kidney transplantation. According to Joseph M. Grinyó, MD, PhD, and colleagues in Buenos Aires, Argentina, these agents may be associated with patient comorbidity via nephrotoxicity and cardiovascular risk (hypertension, hypercholesterolemia, and diabetes mellitus), as well as transplant loss via chronic transplant injury. The researchers contend that there is a need for immunosuppressive agents that control the alloimmune response as effectively as CNIs, but do not have the possible renal and cardiovascular adverse effects.

Some immunosuppressive regimens that avoid or minimize CNI involve the mammalian target of rapamycin (mTOR) inhibitors sirolimus or everolimus; those have been evaluated in earlier prospective studies of recipients of kidney transplant. In those studies, patients who switched from therapy based on CNIs to one based on a mTOR inhibitor had significant improvement in kidney function 12 months after the change compared with patients who continued with treatment with cyclosporine or tacrolimus. However, the patients in the mTOR inhibitor groups were more likely to experience adverse events, particularly dyslipidemia and proteinuria.

The immunosuppressive belatacept selectively inhibits activation of T cells via costimulation blockade. In a recent phase 2 trial, belatacept was studied as conversion therapy in patients maintained on immunosuppression based on CNI (cyclosporine or tacrolimus). The primary outcome of the trial was change in estimated glomerular filtration rate (eGFR) at 12 months, improvement in kidney function from baseline was statistically significant in patients who switched to belatacept-based immunosuppression compared with those who continued CNI therapy (7.0 vs 2.1 mL/min/1.73 m²; P=0.006). Further, there was no association with increased risk for death or transplant loss in the patients who switched therapy.

Among those who remained in the trial beyond 12 months, mean change in eGFR from baseline remained greater than among those who did not switch. Between 12 and 24 months, no patient in the belatacept group experienced acute transplant rejection compared with three patients in the group that did not switch to belatacept.

Dr. Grinyó et al. reported on outcomes at 36 months after randomization in the intention-to-treat population of this study [American Journal of Kidney Diseases. 2017;69(5):587-594]. Of 84 patients treated with belatacept, 74 (88%) were followed up for the full 36 months, as were 72 of the 89 (81%) patients in the CNI group. Reasons for discontinuation prior to the 36-month follow-up in the belatacept group were lack of efficacy (n=2), adverse events (n=1 [polyoma virus-associated nephropathy]), death (n=1) and other (n=1). In the CNI group, 14 patients discontinued treatment: unknown reasons (n=4), withdrawal of consent (n=3), adverse events (n=2 [pulmonary edema and nephropathy, n=1; cellulitis, n=1]), other (n=2), administrative reason (n=1), death (n=1), and lack of efficacy (n=1). There were also 16 patients in the CNI group who switched to belatacept after month 24, as permitted in the study protocol.

At the 36-month mark, the cumulative frequency of serious adverse events was similar for the two groups: 39% (33/84) in the belatacept group and 40% (36/89) in the CNI group. Incident rates of serious infections per 100 person-years of treatment exposure were also similar: 10.21 per 100 person-years in the belatacept group and 9.31 per 100 person-years in the CNI group. However, more patients in the belatacept group had any-grade viral infections compared with those in the CNI group (14.60 vs 11.00 per 100 person-years, respectively). There was no post-transplantation lymphoproliferative disorder reported in either group.

In the belatacept group, mean eGFR increased from month 1 to month 36; there was no increase in the CNI treatment group. At months 12, 24, and 36, mean eGFRs in the belatacept group were 60.3, 62.4, and 62.4 mL/min/1.73 m², respectively. Corresponding eGFRs in the control group were 56.9, 55.0, and 55.6 mL/min/1.73 m², respectively.

Between 12 and 24 months, no patient in the belatacept group experienced acute transplant rejection compared with three patients in the group that did not switch to belatacept.

There was no significant difference in the probability of acute rejection for belatacept (8.38% vs 36.0%; hazard ratio [HR], 2.50; 95% confidence interval [CI], 0.65-9.65; P=.2). The HR for the comparison of belatacept to the CNI group for time to death or transplant loss was 1.00 (95% CI, 0.14-7.07; P=.9).

The researchers cited some limitations to the study, including the small sample sizes, the open-label design of the trial, and the large range of times between transplantation and conversion (6-36 months) which may have confounded the results.

In conclusion, the researchers said, “Despite these limitations, our results suggest that the improvements in kidney function seen in patients who switched from CNI-based to belatacept-based immunosuppression were sustained over 36 months and may help preserve long-term transplant function. This exploratory analysis indicated that switching from a CNI-based to a belatacept-based regimen may represent a safe and effective clinical approach to long-term immunosuppression, one that is being further explored in an ongoing phase 3b trial (clinicaltrials.gov study number NCT01820572).”

TAKEAWAY POINTS

- Results of a phase 2 study among kidney transplant recipients with low immunologic risk who switched form a calcineurin inhibitor (CNI) to belatacept are presented in this article.
- At 6 to 36 months following transplantation, treatment exposure-adjusted incidence rates for serious infections and malignancies were similar between the belatacept group and the CNI group.
- There were no significant differences between the two groups in the probability of acute rejection.

Nephrology Times | July/August 2017
Risk of Hip Fracture and PPI Use in Kidney Transplant Recipients

Increased mortality, decreased mobility, and loss of independence are all associated with hip fracture. For patients with end-stage renal disease (ESRD), the risk of hip fracture is considerably elevated compared with that of the general population. The time immediately following kidney transplantation is particularly high-risk for hip fracture due to pre-existing chronic kidney disease and the associated mineral bone disease, corticosteroid exposure, and osteoporosis.

Proton pump inhibitors (PPIs) are frequently prescribed as peptic ulcer prophylaxis in the period immediately following kidney transplantation. A significant proportion of kidney transplant recipients remain on PPI therapy beyond the immediate post-transplantation period. Omeprazole is the seventh, sixth, and fifth most prescribed drug in the first, second, and third year post-transplantation, respectively.

Use of PPIs has been linked to increased risk for fracture in the general population. However, according to Colin R. Lenihan, MB, BS, and colleagues, there are few data on the link between use of PPIs and the risk of hip fracture in the kidney transplantation population. The researchers recently conducted a retrospective nested matched case-control study to challenge the null hypothesis of no association between PPI use and post-transplantation hip fracture in a contemporary cohort of kidney transplant recipients in the United States. Study results were reported in the American Journal of Kidney Diseases [2017;69(5):595-601].

Eligible study participants were all first-time kidney transplant recipients recorded and contributing to the US Renal Data System while having a functioning kidney transplant January 1, 2007, to December 31, 2011. The researchers identified 231 cases of hip fracture that met the stated inclusion and exclusion criteria. Those cases were matched with 15,575 controls; the number of matched controls per case ranged between one and 225, with a median of 56.

There was a higher prevalence of diabetes mellitus, cardiovascular disease, cerebrovascular disease, arrhythmia, and rheumatologic disease among cases than controls. Use of steroids, mammalian target of rapamycin inhibitors, cyclosporine, azathioprine, and bisphosphonate was higher among cases than controls. The mean difference in age between cases and controls was 1.7 years; mean difference in time since transplantation was 0.3 years, reflecting good matching within the prespecified bounds (3 years for age and 1 year for time since transplantation).

In the 12 months prior to the index date, 65.4% of cases and 57.4% of controls filled a prescription for a PPI. 34.6% of cases and 28.9% of controls filled prescriptions for a PPI covering at least 292 of 365 days (>80%) before the index date (defined as higher PPI users).

Unadjusted odds ratios (ORs) of hip fracture associated with any, lesser, and higher PPI use resulted in nonsignificant results (P > .99). Following adjustment for baseline demographic, clinical, and pharmacologic variables, analysis showed an association between hip fracture status and any and high PPI use (ORs, 1.39; 95% CI, 1.04-1.84, and 1.41; 95% CI, 1.02-1.95, respectively). The researchers cited some limitations to the study, including the retrospective design that creates the possibility of residual confounding and the possibility that some PPI users may have been missed due to the availability of over-the-counter PPIs. In addition, some data were missing, including (1) the use of alternative peptic ulcer prophylaxis/anti–gastroesophageal reflux agents; (2) use of calcium, vitamin D, and other treatments related to bone health; and (3) smoking status.

The researchers summarized their findings by saying, “We found that PPI use was associated with increased odds of hip fracture in kidney transplant recipients. Our findings argue for a more judicious approach to prescription of PPIs in this population.”
**KDIGO Issues Updated Guidelines for Treatment of CKD-MBD**

In late June, the Kidney Disease Improving Global Outcomes (KDIGO) updated its Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). The update amends the 2009 KDIGO Clinical Practice Guideline and includes revised positions on standards of care for the treatment of secondary hyperparathyroidism (SHPT) in patients with CKD stage 3 or 4.

Therapies with calcitriol and (1a-hydroxylated) vitamin D are no longer suggested for routine use. Under the new guidelines, those therapies should be reserved to patients with CKD stage 4 or 5 with severe, progressive hyperparathyroidism. According to the guideline, recent randomized clinical trials of calcitriol and its analogs did not result in improvement in outcomes, but did demonstrate increased risk of hypercalcemia. KDIGO said the risk-benefit ratio was no longer favorable for routine usage in patients with CKD stage 3 or 4. In addition, supplementation of nutritional vitamin D with ergocalciferol or cholecalciferol has not been proven as effective treatment for SHPT.

The updated guideline acknowledged extended release calcifediol (Rayaldee®) as a novel vitamin D prohormone, noting that it increased serum levels of 25-hydroxyvitamin D and lowered PTH in patients with stage 3 or 4 CKD. Rayaldee is the first and only extended-release prohormone approved by the FDA to treat SHPT; its safety profile is similar to that of placebo.

“**The updated guideline represents a needed shift in the way nephrologists managed secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease. SHPT is one of the most common complications of CKD, and, unfortunately, it has also been historically difficult to treat due to a lack of an effective and appropriate FDA-approved treatment option.”**

—Michael J. German, MD, OPKO Health

In a press release from OPKO Health, developers of Rayaldee, Michael J. German, MD, said, “The updated guideline represents a needed shift in the way nephrologists managed secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease. SHPT is one of the most common complications of CKD, and, unfortunately, it has also been historically difficult to treat due to a lack of an effective and appropriate FDA-approved treatment option. Having this updated guidance and the availability of an option like Rayaldee are significant advancements for both patients and providers managing this complex disease.”

Charles W. Bishop, PhD, CEO of the OPKO Health Renal Division, said, “The updated KDIGO guideline highlights the unmet needs that exist in the treatment of SHPT, and we are working with physicians and other healthcare professionals to address these needs with Rayaldee.”

**Educational Partnership between Cricket Health and American Kidney Fund**

Cricket Health and the American Kidney Fund (AKF) have announced a collaborative initiative to provide education and support to patients with advanced stage chronic kidney disease (CKD) and end-stage renal disease (ESRD). One hundred individuals in AKF’s patient network will voluntarily enroll into Cricket Health’s online kidney care platform. Those 100 patients represent the initial group of program participants; Cricket Health is refining the program for a wider commercial rollout to providers and health plans who are looking for an education and care management program for patients with CKD and ESRD.

In a dual press release, LaVarne A. Burton, president and chief executive officer of AKF, said, “As organizations deeply committed to the best health outcomes for the patients we serve, AKF and Cricket Health are logical partners in helping bring technology and patients together. Cricket Health’s platform is a great complement to the patient-focused programs and services we provide.”

Vince Kim, co-founder of Cricket Health, said, “The lack of timely and comprehensive CKD education represents an enormous missed opportunity to increase rates of home dialysis therapies and kidney transplantation among eligible patients. We are excited to work with a leading advocate like the American Kidney Fund to enhance the quality of life for these patients and demonstrate a better way to provide patients the tools and resources necessary to make enduring decisions about the care and management of their disease.”
Chronic Kidney Disease Affects 15% of US Population

The National Kidney Foundation issued a press release highlighting results of a Centers for Disease Control and Prevention study analyzing data from the 2011-2014 National Health and Nutrition Examination Survey and the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation. The study found that the number of Americans affected by CKD is higher than previously estimated. CKD affects 15% of the adult population in the United States. Kevin Longino, NKF Foundation CEO and a kidney transplant patient, said, “Thirty million Americans are affected by chronic kidney disease and most do not even know they have it. Additional federal resources must be allocated towards increasing public awareness about the disease and advancing programs targeted towards prevention and early detection.”

Other findings included in the release reveal that women are more likely than men to be affected by CKD (16% vs 13%); however, men are more likely than women to progress to end-stage renal disease (ESRD). Approximately 15% of Hispanics have CKD and Hispanics are 35% more likely to progress to ESRD compared with non-Hispanics. CKD is also estimated to be more common in non-Hispanic blacks than in non-Hispanic whites (18% vs 13%).
National Kidney Foundation and HealthUnlocked Announce Online Partnership

In late June, the National Kidney Foundation (NKF) and HealthUnlocked, a website that increases patient engagement to improve health outcomes, announced a collaboration that includes four new online communities providing help, support, and information to people with, at risk for, or affected by kidney disease. The communities will provide support and information on kidney disease, dialysis, living donors, and transplant recipients.

The chief medical officer of HealthUnlocked, Matt Jameson Evans, MD, said in a NKF press release, “Support, help, and information is invaluable to people living with kidney disease or at risk of developing it. This new collaboration will create a safe space for people to ask questions, and reach out to others. By coming to one of these communities, the millions of people affected by kidney disease will find important support from others going through similar experiences.”

Kathryn Pucci, senior vice president, education and programs, at NKF, added, “We are pleased to announce the launch of NKF’s online communities: Early Stage CKD, Dialysis, Transplant, and Living Donation in collaboration with HealthUnlocked. Offering patients and their families a safe outlet to share information, successes, and concerns is at the heart of NKF’s mission.”

Agreement to Provide Vadadustat to US

Akebia Therapeutics, Inc., and Vifor Pharma Group announced an exclusive license agreement to market vadadustat to Fresenius Medical Care dialysis clinics in the United States upon US FDA approval. Vadadustat is an oral hypoxia-inducible factor (HIF) stabilizer in phase 3 development for the treatment of anemia associated with chronic kidney disease.

In a press release from Akebia, Stefan Schulze, president of the executive committee and chief operating officer of Vifor Pharma, said, “Vadadustat could represent a significant advancement in the treatment of renal anemia associated with chronic kidney disease. This transaction strengthens the nephrology product portfolio of Vifor Pharma, and is consistent with our ongoing commitment to deliver innovative products that can improve the lives of patients suffering with chronic kidney disease.”

The terms of the agreement call for Vifor Pharma to exclusively distribute vadadustat to Fresenius Medical Care North America for use solely within its dialysis facilities in the United States to meet their need for an HIF-based treatment for anemia associated with CKD.

John P. Butler, president and chief executive officer of Akebia, said, “This agreement provides the opportunity to build greater commercial momentum for vadadustat in the United States rapidly upon launch. We are pleased that Vifor Pharma has selected vadadustat as its exclusive product for distribution to Fresenius Medical Care, one of the largest dialysis providers. We believe that this commitment provides significant further validation of vadadustat’s potential.”

Iron-deficiency anemia in CKD is different.

Is it time for a new school of thought?

In CKD, progressive loss of renal function along with chronic inflammation leads to:

- High concentrations and reduced clearance of hepcidin
  - Impaired intestinal iron absorption
  - Restricted release of iron from storage

Can different thinking help us address these challenges for iron-deficiency anemia in CKD?

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Abstract Roundup

CHRONIC KIDNEY DISEASE

Benefits of Phosphorus Binder Use among Non-Dialysis CKD Patients

It is unknown whether the benefits of phosphorus binders extend to patients with chronic kidney disease (CKD) but without end-stage renal disease. In a retrospective cohort study conducted by Simran Bhandari, MD, and colleagues, the researchers sought to evaluate phosphorus binder use and compare risk of mortality between patients prescribed and not prescribed binders in a large diverse non-dialysis dependent CKD population.

Among 10,165 study patients, 27% (n=2733) received phosphorus binders. Using a traditional multivariable model, compared with the group not receiving phosphorus binders, the hazard ratio [HR] for mortality among the binder group was 0.86 (95% confidence interval [CI], 0.79-0.94). Results from an inverse probability of treatment-weighted model, the HR in the binder group was 0.86 (95% CI, 0.80-0.93). When patients who were prescribed binders >180 days following the index date, there was no difference in mortality between the binder group and the non-binder group.

The researchers said, “Our findings from a real-world clinical environment revealed that 27% of hyperphosphatemic non-dialysis CKD patients were prescribed binders. They also had a lower risk of mortality compared to those not prescribed phosphorus binders. However, the lower mortality risk was not observed when we accounted for immortal time bias. Whether phosphorus binder use in CKD improves survival remains to be determined.”

Phase 2a Trial of Vadadustat for Anemia Secondary to CKD

There are limited therapeutic options for the treatment of anemia secondary to chronic kidney disease (CKD). Edouard Martin, MD, and colleagues reported results of a phase 2a, multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial of vadadustat (AKR-6548), an oral hypoxia-inducible factor prolyl-hydroxylase domain (HIF-PHD) inhibitor. The trial (NCT01381094) is being conducted to assess the use of vadadustat in patients with anemia secondary to CKD stage 3 or 4.

Patients were evenly randomized to five groups based on dose: 240, 370, 500, or 630 mg of oral vadadustat once daily, or placebo. All participants received 50 mg of supplemental oral iron once daily. The primary end point was the mean absolute change in hemoglobin from baseline to the end of treatment.

The study randomized 93 subjects. Compared with placebo, there was a significant increase in hemoglobin with vadadustat after 6 weeks in a dose-dependent manner (analysis of variance; P<.001). Vadadustat increased the total iron-binding capacity and decreased concentrations of ferritin and hepcidin. Safety was similar between the groups treated with vadadustat and the group treated with placebo.

In conclusion, the researchers said, “Vadadustat increased hemoglobin levels and improved biomarkers of iron mobilization and utilization in patients with anemia secondary to stage 3 or 4 CKD. Global multicenter, randomized phase 3 trials are ongoing in non-dialysis dependent and dialysis-dependent patients.”

Serum Uric Acid and Total Bilirubin Associated with Renal Dysfunction
International Urology and Nephrology. doi:10.1007/s11239-017-1633-8

In a study conducted in a remote village in Japan designed to determine whether serum uric acid and total bilirubin produce an additive interactive for the risk of renal dysfunction, Ryuichi Kawamoto, MD, PhD, and colleagues examined the relationship between serum uric acid and total bilirubin and renal function by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study Group equation.

Results of stepwise multiple regression analysis using eGFR as an objective variable showed significant and independent associations between serum uric acid, age, drinking status, and the presence of antihypertensive medication and eGFR; there was no association between total bilirubin and eGFR. The group in the highest tertile of serum uric acid, total bilirubin was significantly and independently associated with eGFR; however, in the group with the lowest to middle tertile of serum acid, there was no association between total bilirubin and eGFR. The interaction between serum uric acid and total bilirubin, as well as age, drinking status, presence of antihypertensive medication, serum uric acid, and total bilirubin, was a significant and independent determinant for eGFR.

“Our data demonstrated that low total bilirubin could be important as a potential risk factor for renal dysfunction in those with high serum uric acid,” the researchers said.

DIALYSIS

Febuxostat Improves Endothelial Dysfunction in Dialysis Patients
American Journal of Nephrology. 2017;45(5):452-459

In patients with end-stage renal disease, endothelial dysfunction is a major risk factor for cardiovascular disease. Previous studies have shown a positive effect of febuxostat in improving endothelial dysfunction; however, there are few data on the effect of febuxostat in patients on maintenance hemodialysis.

Febuxostat is a novel xanthine oxidase inhibitor. Mona Alshahawey and colleagues recently conducted a prospective, placebo-controlled, block-randomized, double-blinded study to assess the effect of oral febuxostat on endothelial dysfunction in patients on hemodialysis. Fifty-seven patients were randomized to receive either 40 mg of febuxostat three times a week or placebo. At baseline and at the end of the 2-month study, serum asymmetric dimethylarginine, serum uric acid, and serum high sensitivity C-reactive protein were measured. At baseline and again at the end of the study, serum albumin aminotransferase, serum aspartate aminotransferase, and the occurrence of pancreatitis were tested as safety parameters.

In the febuxostat group, there was a significant decrease in serum uric acid (from 7.5 to 5.1 mg/dL; there was no significant change in the placebo group. The febuxostat group also had significant decreases in serum asymmetric dimethylarginine level (1.027 to 0.944 μmol/L) and serum high sensitivity C-reactive protein level (12.5 to 12.2 mg/L). There were no differences in the prespecified safety markers between the two groups.

The researchers said, “Febuxostat appears to improve hyperuricemia and endothelial dysfunction and ameliorate inflammation in hemodialysis patients with no safety concerns.”

GERIATRIC NEPHROLOGY

Factors Associated with Progression of CKD in Elderly Patients
International Urology and Nephrology. 2017;49(6):1033-1040

There has been a steady rise in the prevalence of chronic kidney disease (CKD) in the elderly population. Pradeep Arora, MD, and colleagues recently conducted an observational study designed to examine the rate of CKD in the elderly and the factors associated with disease progression to help identify patients with CKD likely to progress to end-stage renal disease.

The study included 4562 patients >65 years of age who had two outpatient estimated glomerular filtration rates (eGFRs) of <60 mL/min/1.73 m² a minimum of 90 days apart with no intervening eGFR >60 mL/min/1.73 m² at Veterans Administration healthcare facilities. Exclusion criteria included eGFR <15 mL/min/1.73 m². The annual rate of eGFR decline was examined and classified as <1 mL/min/1.73 m², 1 to 4 mL/min/1.73 m², and >4 mL/min/1.73 m².

Mean age of participants was 77.2 years, 24.3% had diabetes, and 4.3% had proteinuria. Multivariable mixed model analyses found an association between a significantly increased rate of progression of CKD and increasing age, body mass index, and the presence of cardiovascular disease, diabetes mellitus, and proteinuria. There was an inverse association of serum albumin and...
hemoglobin with progression of CKD. “CKD progresses at a slower rate in the elderly population. We have identified risk factors associated with an increased risk of progression of CKD in the elderly. This may help to improve health care planning and resource utilization,” the researchers said.

**HYponatremia**

**Management of Thiazide-Associated Hyponatremia Is Often Poor American Journal of Nephrology, 2017:45(5):420-430**

Use of thiazide diuretics may result in hyponatremia, a potentially life-threatening adverse side effect. Volker Burst, MD, and colleagues recently conducted a sub-analysis of the Hyponatremia Registry database that focused on current management practices of hyponatremia related to thiazide use and compared differences between thiazide-associated hyponatremia and syndrome of inappropriate antidiuretic hormone secretion.

The researchers analyzed data on 477 patients from 225 sites in the United States and Europe. All patients were receiving a thiazide diuretic. Of the 477 patients, 118 met criteria for true thiazide-induced hyponatremia.

In only 57% of diagnoses of thiazide-associated hyponatremia was the diuretic withdrawn; in those patients, the median rate of sodium change was significantly higher than in those who continued treatment with thiazide. The most frequently employed therapies were isotonic saline (29.6%), fluid restriction (19.9%), a combination of those two (8.2%), and hypertonic saline (5.2%). The greatest change in sodium was achieved with hypertonic saline, followed by a combination of fluid restriction and normal saline and normal saline alone. Fluid restriction was markedly less effective.

In conclusion, the researchers said, “Despite its high incidence and potential risks, the management of thiazide-associated hyponatremia is often poor. Immediate withdrawal of the thiazide is crucial for treatment success. Hypertonic saline is most effective in correcting hyponatremia but associated with a high rate of overly rapid correction. We could not establish a diagnostic laboratory-based test to differentiate thiazide-induced hyponatremia from the syndrome of inappropriate antidiuretic hormone secretion.”

**TRANSPLANTATION**

**Circulating HLA/DSAs Associated with Premature and Accelerated Allograft Fibrosis Kidney International. http://dx.doi.org/10.1016/j.kint.2017.03.033**

One of the challenges for improving long-term transplantation outcomes is addressing the causes of kidney allograft-accelerated aging. Clément Gosset, MD, and colleagues recently conducted a study to investigate the role of circulating donor-specific anti-HLA antibodies (HLA-DSAs) in the development and progression of kidney allograft fibrosis with inclusion of traditional risk factors for allograft fibrosis.

The prospective study enrolled 1539 consecutive recipients of kidney transplant at two centers. The researchers examined interstitial fibrosis and tubular atrophy (IF/TA) in biopsies performed at one year post-transplantation. The HLA-DSAs and all traditional indicators of IF/TA were recorded at the time of transplantation and again within the first year following transplantation, identifying 498 patients with severe IF/TA.

Following inclusion of 37 determinants, there was a significant association between severe IF/TA and HLA-DSAs (adjusted odds ratio, 1.53; 95% confidence interval, 1.16-2.01).

The primary contributor was HLA-DSAs (11% of cases), followed by T-cell mediated rejection (9% of cases), calcineurin-inhibitor toxicity (8% of cases), acute tubular necrosis (6% of cases), pyelonephritis (5% of cases), and BK virus-associated nephropathy (4% of cases).

Compared with 344 patients with severe IF/TA without HLA-DSAs, 144 patients with HLA-DSA-associated severe IF/TA showed significantly increased microvascular inflammation, transplant glomerulopathy, C4d deposition in capillaries, and decreased allograft survival. Compared with 1161 patients without HLA-DSAs in the one-year post-transplantation biopsies, 378 patients with post-transplant HLA-DSAs exhibited significantly accelerated progression of IF/TA. “Circulating HLA-DSAs are major determinants of premature and accelerated allograft fibrosis acting independently of traditional risk factors and antibody-mediated rejection,” the researchers said.

**Recurrent Glomerulonephritis Significant Cause of Allograft Failure**


Patients who experience recurrent glomerulonephritis following kidney transplantation are at risk for negative graft outcomes. Penelope J. Allen, MD, and colleagues recently conducted a study utilizing 30-year data from the Australia and New Zealand Dialysis and Transplant Registry. Using Cox proportional hazard and competing risk modeling, the researchers determined the incidence, risk factors, and outcomes of recurrent glomerulonephritis in recipients of kidney transplants.

The study followed 6597 transplant recipients with biopsy-proven glomerulonephritis for a total of 51,871 person-years (mean, 7.7 years). The four most common types of glomerulonephritis were: (1) IgA nephropathy, n=2501; (2) focal segmental glomerulosclerosis (n=1403); (3) membranous (n=876); and (4) membranoproliferative (n=387). Among those patients, recurrence was reported in 479 of 4637 patients; of those, 212 experienced allograft failure due to the recurrence. There was an association between older age at time of transplantation and lower risk of recurrence (adjusted hazard ratio [per year increase], 0.96; 95% confidence interval, 0.95-0.97).

For patients with recurrent membranoproliferative glomerulonephritis, the 5-year graft survival was 30%; for those with focal segmental glomerulosclerosis, IgA, and membranous nephropathy, 5-year graft survival was 57% to 59%. Among recipients with recurrent disease, the risk of losing their allograft was twice that of those without recurrent disease (adjusted hazard ratio, 2.04).

In conclusion, the researchers said, “Recurrent glomerulonephritis remains a significant cause of graft loss in transplant recipients.”
Recognizing that key differences exist in the reimbursement of services for acute kidney injury (AKI) patients, the Centers for Medicare & Medicaid Services (CMS) issued important clarifications in June that significantly impact physician and outpatient dialysis facility claims.

End-stage renal disease (ESRD) Conditions for Coverage, the Low Volume Payment Adjustment, home dialysis, physician services, payment for erythropoietin stimulating agents (ESAs), telehealth, modifiers, value codes, condition codes, and occurrence codes were all impacted by Change Request 9987 and the June 19 update to MLN Matters codes, condition codes, and occurrence codes were all impacted by Change Request 9987 and the June 19 update to MLN Matters MM9598.

For outpatient dialysis facilities, the information required on claims for AKI patients will be significantly different from claims for ESRD patients. For example, the heights and weights of AKI patients need not be reported on claims. While reimbursement for ESRD patients vary because of each patient’s height and weight, there are no such payment adjustments related to an AKI patient’s height and weight.

Other clarifications noted that outpatient dialysis facilities no longer need to report values and/or modifiers for vascular access, urea reduction ratios, hemoglobin, or hematocrits.

ESAs given to AKI patients should be billed by outpatient dialysis facilities using non-ESRD Healthcare Common Procedure Coding System codes. Also, CMS clarified that there will be no separate payment for ESAs for AKI patients because it is included in the bundled rate for ESRD patients, which is the basis for the amount reimbursed for services provided to AKI patients.

CMS also noted that AKI patients do not qualify for reimbursement for telehealth services at this time, “unless other criteria are met.”

To find resources for your state, a simple internet search for recoupment laws by state can point you in the right direction.

Physicians received good news as CMS confirmed in the update that they will reimburse for services provided to AKI patients in ESRD facilities as well as in physician offices. Depending on how physician visits to patients in ESRD facilities are captured and reported to billing staff, physicians and billers may want to flag visits to AKI patients to ensure that billers use the correct codes for these visits.

STATUTE OF LIMITATIONS ON INSURANCE REFUND OR RECOUPMENT

Over the years, we have worked with providers who receive refund notices from payers for claims paid months or even years earlier. These refund notices often come as a complete surprise and are frequently due to some kind of internal issue experienced by the payer. Examples include errors in the payer’s claim processing system and internal audits or reviews that indicate a claim should have been paid at a different rate or not at all. Of course, providers have long since spent the money received and may be financially unprepared to pay back tens or hundreds of thousands of dollars demanded by the payer. Fortunately, your state’s laws regarding insurance refunds and your contracts with payers may be able to save you both headaches and money.

Some states have laws that place a statute of limitations on how much time payers have to request refunds for paid claims. The length of time varies for each of these states and can be as short as 6 months or as long as 5 years. Some of the state laws include exceptions to their time limits, such as coordination of benefit errors, fraud, or intentional misconduct by the provider.

To find resources for your state, a simple internet search for recoupment laws by state can point you in the right direction. Many states also have a department of insurance with customer service representatives that can assist in finding the state documents that provide the details of the law.

However, regardless of whether your state has a statute of limitations, you can always protect yourself by carefully contracting with payers. Whenever you negotiate a payer contract, make sure the contract specifies acceptable time limits for the payer to request refunds or recoup payments.

Payer contracts can also work against you, even in states with statutes of limitations regarding payer recoupment. If you agreed to longer recoupment/refund times in your contract, such clauses can lessen or even nullify the protections provided by the laws in your state. Whenever you negotiate a new or updated payer contract, carefully review any clauses regarding the length of time the payer has to request refunds or recoup payments. If no such language exists in the contract, you may want to include a time limit in order to protect yourself.

Rick Collins is the chief operating officer and Sarah Tolson is the director of training for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD facilities, nephrology practices, and vascular access. Your questions are welcome and they can be reached at rcollins@sceptremanagement.com, stolson@sceptremanagement.com, or 801.775.8010.
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1 In Clinical Trials vs. Placebo. Triferic® [Package Insert], Rockwell Medical, Wixom, MI, September 2015.

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